2 Postapproval Changes to Semisolid Drugs

To ensure continuing product quality and performance characteristics of the semisolid topical formulations, regulatory approvals are required for changes to

1. Components or composition
2. Manufacturing (process and equipment)
3. Scale up/scale down of manufacture
4. Site of manufacture of a semisolid formulation during the postapproval period

It is important to define

1. The levels of change
2. Recommended chemistry, manufacturing, and controls tests to support each level of change
3. Recommended *in vitro* release tests or *in vivo* bioequivalence tests to support each level of change
4. Documentation to support the change

The effect that scale-up and postapproval changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*. For scale-up and postapproval changes submissions, the following points should also be considered:

A. In most cases, except those involving scale up, stability data from pilot scale batches will be acceptable to support the proposed change.
B. Where stability data show a trend toward potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative prechange batch be submitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.
C. A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on either the first or first three (see below for details) production batches and to report the results in subsequent annual reports.

Definition of level 1 changes are those that are unlikely to have any detectable effect on formulation quality and performance. Examples:

A. Deletion or partial deletion of an ingredient intended to affect the color, fragrance, or flavor of the drug product.
B. Any change in an excipient up to 5% of approved amount of that excipient. The total additive effect of all excipient changes should not be more than 5%. Changes in the composition should be based on the approved target composition and not on previous level 1 changes in the composition. A change in diluent (q.s. excipient) caused by component and composition changes in excipient may be made and is excluded from the 5% change limit.
C. Change in a supplier of a structure forming excipient that is primarily a single chemical entity (purity 95%) or change in a supplier or technical grade of any other excipient.

Definition of level 2 changes are those that could have a significant effect on formulation quality and performance. Examples:

A. Changes of >5% and <10% of approved amount of an individual excipient; the total additive effect of all excipient changes should not be more than 10%
B. Changes in the composition should be based on the approved target composition and not on previous level 1 or level 2 changes in the composition
C. Changes in diluent (q.s. excipient) caused by component and composition changes in excipients are acceptable and are excluded from the 10% change limit
D. Change in supplier of a structure forming excipient not covered under level 1

E. Change in the technical grade of structure-forming excipient
F. Change in particle size distribution of the drug substance if the drug is in suspension

Definition of level 3 changes are those that are likely to have a significant effect on formulation quality and performance. Examples:

A. Any qualitative and quantitative changes in an excipient beyond the ranges noted in level 2 change.
B. Change in crystalline form of the drug substance, if the drug is in suspension

I. PRESERVATIVE

For semisolid products, any change in the preservative may affect the quality of the product. If any quantitative or qualitative changes are made in the formulation, additional testing should be performed. No *in vitro* release documentation or *in vivo* bioequivalence documentation is needed for preservative changes.

II. MANUFACTURING CHANGES

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself. A level 1 change is a change from nonautomated or nonmechanical equipment to automated or mechanical equipment to transfer ingredients or a change to alternative equipment of the same design and operating principles. A level 2 change is a change in equipment to a different design or different operating principles or a change in type of mixing equipment, such as high shear to low shear and vice versa. No level 3 changes are anticipated in this category.

III. PROCESS

Level 1 changes include changes such as rate of mixing, mixing times, operating speeds, and holding times within approved application ranges, in addition to the order of addition of components (excluding actives) to either the oil or water phase. Level 2 changes include changes such as rate of mixing, mixing times, rate of cooling, operating speeds, and holding times outside approved application ranges for all dosage forms in addition to any changes in the process of combining the phases. No level 3 changes are anticipated in this category.

Batch Size (Scale Up or Down)

The minimum batch size for the NDA pivotal clinical trial batch or the ANDA/AADA biobatch is at least 100 kg or 10% of a production batch, whichever is larger. All scale changes should be properly validated and may be inspected by appropriate agency personnel. Level 1 changes in batch size are those up to and including a factor of 10 times the size of the pivotal clinical trial or biobatch, where the equipment used to produce the test batch or batches is of the same design and operating principles, the batch or batches are manufactured in full compliance with current good manufacturing practice (CGMPs), and the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch or batches and on the full-scale production batch or batches. Level 2 changes in batch size are those from beyond a factor of 10 times the size of the pivotal clinical trial or biobatch, where the equipment used to produce the test batch or batches is of the same design and operating principles, the batch or batches is manufactured in full compliance with CGMPs, and the same SOPs and controls, as well as the same formulation and manufacturing procedures, are used on the test batch or batches and on the full-scale production batch or batches. No level 3 changes are anticipated in this category.

IV. MANUFACTURING SITE

Manufacturing site changes consist of changes in location in the site of manufacture, packaging and filling operations, or testing for both company-owned and contract manufacturing facilities, and they do not include any other level 2 or 3 changes; for example, changes in scale, manufacturing (including process or equipment), and components or composition. New manufacturing locations should have had a satisfactory CGMP inspection within the past 2 years. A stand-alone analytical testing laboratory site change may be submitted as a Changes Being Effected Supplement if the new facility has a current and satisfactory CGMP compliance profile with the FDA for the type of testing operation in question. The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with CGMPs, and a full description of the testing to be performed by the testing lab. If the facility has not received a satisfactory CGMP inspection for the type of testing involved, a prior approval supplement is recommended. No stability data are needed for a change in a stand-alone analytical facility. Level 1 changes consist of site changes within a single facility where the same equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. "Common" is defined as employees already working on the campus who have suitable experience with the manufacturing

process. Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where similar equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Level 3 changes consist of a site change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a level 3 change, similar equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site. Changes should not be made to the manufacturing batch records except when consistent with other level 1 changes. Administrative information, location, and language translation may be revised as needed. Any change to a new contract manufacturer also constitutes a level 3 change.